

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

To:

see form PCT/ISA/220

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/GB2004/002341

International filing date (day/month/year)
02.06.2004

Priority date (day/month/year)
02.06.2003

International Patent Classification (IPC) or both national classification and IPC
C12N15/12, C07K14/435, C12N15/11, C12N15/62, A61K38/17, G01N33/68

Applicant
EVOLUTEC LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☒ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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Box No. II Priority

1. ☐ The following document has not been furnished:
- ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).
 - ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).
- Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. ☒ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.
4. Additional observations, if necessary:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 32,34,35,37-40 with respect of industrial applicability

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 32,34,35,37-40
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☒ See separate sheet for further details

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1-7
Inventive step (IS)	Yes: Claims	
	No: Claims	1-7,17-21,24-40
Industrial applicability (IA)	Yes: Claims	1-31,33,36
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 32,34,35,37-40 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents :

- D1: MCKENZIE R ET AL: "Regulation of complement activity by vaccinia virus complement-control protein." THE JOURNAL OF INFECTIOUS DISEASES. DEC 1992, vol. 166, no. 6, December 1992 (1992-12), pages 1245-1250, XP008038345 ISSN: 0022-1899
- D2: ASGHAR S S ET AL: "Inhibition of complement by a series of substituted 2-aryl-1,3-indandiones: interaction with the fifth component of complement." MOLECULAR IMMUNOLOGY. MAY 1986, vol. 23, no. 5, May 1986 (1986-05), pages 459-465, XP002305197 ISSN: 0161-5890
- D3: WHITE K L JR ET AL: "Suppression of mouse complement activity by contaminants of technical grade pentachlorophenol." AGENTS AND ACTIONS. JUL 1985, vol. 16, no. 5, July 1985 (1985-07), pages 385-392, XP008038344 ISSN: 0065-4299
- D4: BARANDA J A ET AL: "Purification, N-terminal sequencing and diagnostic value of the major antigens of Ornithodoros erraticus and O. moubata." VETERINARY PARASITOLOGY. JAN 2000, vol. 87, no. 2-3, January 2000 (2000-01), pages 193-206, XP002305200 ISSN: 0304-4017
- D5: ASTIGARRAGA A ET AL: "Host immune response evasion strategies in Ornithodoros erraticus and O. moubata and their relationship to the

development of an antiargasid vaccine." PARASITE IMMUNOLOGY. SEP 1997, vol. 19, no. 9, September 1997 (1997-09), pages 401-410, XP008038693 ISSN: 0141-9838

D6: KELLER P M ET AL: "Cloning of the cDNA and expression of moubatin, an inhibitor of platelet aggregation." THE JOURNAL OF BIOLOGICAL CHEMISTRY. 15 MAR 1993, vol. 268, no. 8, 15 March 1993 (1993-03-15), pages 5450-5456, XP002305201 ISSN: 0021-9258

D7: WO 93/17099 A (MERCK & CO INC) 2 September 1993 (1993-09-02)

D8: MANS BEN J ET AL: "Pathogenic mechanisms of sand tampan toxicoses induced by the tick, Ornithodoros savignyi." TOXICON : OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY ON TOXINOLOGY. JUL 2002, vol. 40, no. 7, July 2002 (2002-07), pages 1007-1016, XP002305202 ISSN: 0041-0101

D9: MANS B J ET AL: "Identification of putative proteins involved in granule biogenesis of tick salivary glands." ELECTROPHORESIS. MAY 2001, vol. 22, no. 9, May 2001 (2001-05), pages 1739-1746, XP002305203 ISSN: 0173-0835

The present application relates to the provision of the complement inhibitor of C5 activation, with the molecular sequence data from fig.4 , isolated from soft tick Ornithodoros moubata .It inhibits both the classical and alternative pathways of complement activation .

1. Novelty(Article 33.2 PCT)

D1 discloses the regulation of complement activity by the vaccinia virus complement-control protein. The complement 3 convertase is inhibited . The complement inactivators pentachlorophenol worked on both the alternative and classical complement pathways . VCP was bound by C4b and C3b and served as a cofactor with factor I in cleaving these two molecules. VCP inhibited the formation and accelerated the decay of the classical C3 convertase. It also accelerated decay of the alternative pathway convertase.
(see the abstract)

D2 discloses the inhibition of complement by a series of substituted 2-aryl-1,3-indandiones: interaction with the fifth component of complement. Complement 5 is inhibited . Drug effects on complement activation is measured .The complement inactivators indandiones worked on both the alternative and classical complement pathways .The inhibition in the complement cascade appeared to be at C5. (see the abstract)

D3 discloses the suppression of mouse complement activity by contaminants of technical grade pentachlorophenol. Complement 5 is inhibited . The complement inactivators pentachlorophenol worked on both the alternative and classical complement pathways . (see the abstract)

In view of D1-D3 , the subject-matter of claims 1-7 is not new.

2. Inventive step(Article 33.3 PCT)

D4 discloses the N-terminal sequencing of major antigens of *Ornithodoros erraticus* and *O. moubata* . The molecular sequence data N-terminus region of the 20A1 antigen from *O. moubata* is EENQRGKGMLGSTAASVAVF and shares 46.2% homology with the alpha-chain of the C3 component of rabbit complement .

It discloses that the SGE-2 from *O. Moubata* is powerful inhibitor of complement activation. The SGE-2 are obtained by simple freeze thawing of salivary glands of the species of interest and contains all the salivary components (antigenic and non-antigenic) that the parasite injects into their host .

However whether the 20A1 antigen is indeed responsible for the complement inhibition has not been elucidated . (see the abstract , page 202 third paragraph and page 205 second and third paragraph)

D5 discloses the host immune response evasion strategies in *Ornithodoros erraticus* and *O. moubata* and their relationship to the development of an anti-gasid vaccine. In particular , the salivary gland extract (SGE-2) from *Ornithodoros erraticus* and *O. moubata* showed anticomplement action (see the abstract and fig.5)

D6 & D7 disclose the cloning of a platelet aggregation inhibitor, moubatin from the soft tick *Ornithodoros moubata* , showing 67.451% identity (69.495% ungapped) in 510 nt overlap (1-507:16-513) with seq.1 and 49.112% identity (50.610% ungapped) in 169 aa overlap (1-168:2-166) with seq.2 .(see the abstract , and fig.1 from D6 and

seq.1,2 and claims 1-9 from D7 .

D8 & D9 disclose the major tick salivary gland proteins from the soft tick, *Ornithodoros savignyi*, that are part of the tick Lipocalin family , showing 72.387% identity (75.051% ungapped) in 507 nt overlap (1-507:32-520) with seq.1 and 57.738% identity (59.877% ungapped) in 168 aa overlap (1-168:2-163) with seq.2 (see the abstract and fig.10)

D1 is considered to be the closest prior art.

D1 differs from the present application by the lack of isolation of the tick polypeptide with the molecular sequence from fig.4 , and lack of identification of binding to C5 and inhibition of the C5 convertase cleavage of C5a .

In view of D1 , the problem is the isolation from further complement and alternative complement pathway inhibitory polypeptides .

Knowing the importance of complement pathway inhibitory polypeptides , the person skilled in the art would have had the incentive to solve the problem .

In view of D1 and the prior art D4-D9 , the person skilled in the art would NOT have had reasonable expectation of success in isolating the polypeptide with the molecular sequence from fig.4 from the present application , unexpectedly inhibiting both the classical and the alternative pathway through the binding to C5 and inhibition of the C5 convertase cleavage of C5a . The subject-matter of claims of 8-16, and 22,23 is hence inventive .

However , the person skilled in the art , in relation to vaccinia virus complement-control protein of D1 , would have considered the manufacture of antibodies, fusion proteins , nucleic acids , antisense , vectors, host cells , methods of preparing a complement inhibitor , methods of identifying ligands , the provision of compositions, methods of treating animals , methods of vaccination , the use for the manufacture of a medicament or vaccine as standard designs, use as diagnostic tool or methods of inhibiting the complement pathway . The subject-matter of claims of 17-21,24-40, is hence not inventive .

Comparative study of in vitro inhibition of activation of the classical and alternative pathways of human complement by the magnesium and sodium salts of the anti-inflammatory peptide N-acetyl-aspartyl-glutamic acid (NAAGA).

Feuillard J, Maillet F, Goldschmidt P, Weiss L, Kazatchkine MD.

INSERM U 28, Hopital Broussais, Paris, France.

The inhibitory activity of the sodium salt of the anti-inflammatory peptide N-acetyl-aspartyl-glutamic acid (NAAGA) on activation of the classical and alternative pathways of human complement was compared with that of the clinically used magnesium salt of NAAGA (NAAGA-Mg). Sodium salt of NAAGA (NAAGA-Na) inhibited both pathways of activation in a dose-dependent manner at concentration ranging from 1 to 10 mM by acting on formation and/or function of the C3 convertases as shown by the inhibitory capacity of the peptide on the release of the C3 cleavage fragment C3b and C3a. NAAGA-Na was as effective as NAAGA-Mg in inhibiting classical pathway activation at concentration above 10 mM. NAAGA-Na was more effective than NAAGA-Mg in inhibiting the alternative pathway since the sodium salt did not interfere with Mg-dependent formation of the alternative pathway C3 convertase.

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